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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,952	10/26/2001	Mark H. Tuszynski	041673-2054	7826

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	5

DATE MAILED: 04/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/032,952	Mark Tuszynski
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-12 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is a continuation-in-part of Application No. 09/620,174, filed 7-19-00, which is a continuation-in-part of Application No. 09/060,543, filed 4-15-98. Claims 1-12 are pending and under consideration.

Specification

1. The abstract of the disclosure is objected to because there are more than 150 words in the abstract. Correction is required. See MEP. § 608.01(b).

2. The disclosure is objected to because of the following informalities: There should be the phrase "We claim", "I claim", or "What is claim is" on claim page (page 30 of the specification).

Appropriate correction is required.

Priority

3. The paragraph claiming priority of parent applications on the first sentence of the specification should identify the relationship between Application Nos. 09/620,174 and 09/060,543.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 4-7, 11 and 12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 5-8, 11 and 17 of copending Application No. 09/620,174 ('174). Although the conflicting claims are not identical, they are not patentably distinct from each other because although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 1, 4-7, 11 and 12 are directed to a method for delivery of a therapeutic neurotrophin to targeted defective, diseased or damaged neurons in a mammalian brain comprising delivering a neurotrophic composition comprising a lentiviral vector, such as HIV-1,

encoding neurotrophin into one or more sites within the targeted regions of a mammalian brain, wherein the neurotrophin is expressed in, or within 500 um from, a targeted cell, and no more than about 10 mm from another delivery site, to ameliorate the defect, disease or damage, such as Alzheimer's disease, *in vivo*. Claims 5 and 6 specify the concentration of neurotrophin encoding viral particles and the volume of neurotrophic composition delivered.

Claims 1, 2, 5-8, 11 and 17 of '174 are directed to a method for delivery of a therapeutic neurotrophin to targeted defective, diseased or damaged cholinergic neurons in a mammalian brain comprising delivering a neurotrophic composition comprising a transgene or a viral expression vector, such as a lentiviral vector or HIV-1 vector, encoding a neurotrophin into one or more sites within the targeted regions of a mammalian brain, wherein the neurotrophin is expressed in, or within 500 um from, a targeted cell, and no more than about 10 mm from another delivery site, to ameliorate the defect, disease or damage, such as Alzheimer's disease, *in vivo*.

The viral expression vector as claimed in '174 encompasses lentiviral vector or HIV-1 vector and both the present application and '174 teach using vector expressing human neurotrophin and treating Alzheimer's disease, therefore, the claimed invention of the present application would be obvious for one of ordinary skill at the time of the invention according to the teachings of '174.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 7 recites the limitation "transgene" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claims 8-12 depend on claim 7 but fails to clarify the indefiniteness. Thus, claims 7-12 are rejected under 35 U.S.C. 112 second paragraph.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for direct injection of a composition containing a lentiviral vector expressing a glial cell line-derived neurotrophic factor (GDNF) to a brain to increase flurodopa (FD) uptake in the brain, regeneration of tyrosine hydroxylase (TH)-immunoreactive neuron in lenti-GDNF treated monkey, and functional recovery of hand-reach task from MPTP induced nigrostriatal degeneration in the lenti-GDNF treated monkey, does not reasonably provide enablement for a method for delivery of a therapeutic neurotrophin to targeted defective, disease or damaged neurons in the mammalian brain by delivering a neurotrophic composition comprising a lentiviral vector expressing any neurotrophin to the brain via various administration

routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-12 are directed to a method for delivery of a therapeutic neurotrophin, such as GDNF, to targeted defective, diseased or damaged neurons in a mammalian brain comprising delivering a neurotrophic composition comprising a lentiviral vector, such as HIV-1, encoding neurotrophin into one or more sites within the targeted regions of a mammalian brain, such as substantia nigra or dopaminergic neurons, wherein the neurotrophin is expressed in, or within 500 um from, a targeted cell, and no more than about 10 mm from another delivery site, to ameliorate the defect, disease or damage *in vivo*. Claims 5 and 6 specify the concentration of neurotrophin encoding viral particles and the volume of neurotrophic composition delivered. Claim 7 specifies the treated mammal is a human and the transgene encodes a human neurotrophin. Claims 9-12 specify the human is suffering from Parkinson's disease (PD) or Alzheimer's disease (AD).

The specification discloses direct injection of a composition containing a lentiviral vector expressing GDNF to a monkey brain results in increase in flurodopa (FD) uptake in the brain, and regeneration of tyrosine hydroxylase (TH)-immunoreactive neuron in monkey brain and functional recovery of hand-reach task from MPTP induced nigrostriatal degeneration in the lenti-GDNF treated monkey. The claims encompass using a lentiviral vector expressing any

neurotrophin via various administration routes to ameliorate defective, diseased or damaged neurons in a mammalian brain.

The specification fails to provide adequate guidance and evidence for delivering a neurotrophic composition comprising a lentiviral vector expressing any neurotrophin to a mammalian brain so as to provide therapeutic effects and to ameliorate defective, diseased or damaged neurons in the mammalian brain via various administration routes, such as systemic administration or administration at a site distant from the brain, *in vivo*.

The claims read on gene therapy by using a lentiviral vector expressing any neurotrophin via various administration routes *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of

mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

It was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column).

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the lentiviral vector expressing any neurotrophin to provide therapeutic effects in a patient so as to ameliorate defective, diseased or damaged neurons *in vivo* via various administration routes.

The specification also fails to provide adequate guidance and evidence for how delivering of a neurotrophic composition comprising a lentiviral vector expressing any neurotrophin other than GDNF to a mammalian brain would provide therapeutic effects and ameliorate defective, diseased or damaged neurons in the mammalian brain *in vivo*. The specification indicates that neurotrophin encompass NGF, BDNF, NT-3, NT-4/5, NT-6, CNTF, GDNF, FGF, LIF, the neurturins, persephin, BMPs, the immunophilins, the TGF family of growth factors, the neuregulins, EFG and PDGF etc., (see specification, page 7, lines 20-28). All of the members of neurotrophins are different proteins having different chemical structures and biological functions, for example, BMPs are involved in bone morphogenesis, and TGFs, EGFs and FGFs are involved in non-neural cell proliferations. There is no evidence of record that BMPs, FGF, LIF, the neurturins, persephin, BMPs, the immunophilins, the TGF family of growth factors, the neuregulins, EFG and PDGF etc., can ameliorate defective, diseased or damaged neurons, such as neurons associated with PD or AD, in the mammalian brain *in vivo*. Therefore, one skilled in the art at the time of the invention would not know how to use the claimed lentiviral vector expressing any neurotrophin, such as BMPs, FGF, LIF, the neurturins, persephin, BMPs, the immunophilins, the TGF family of growth factors, the neuregulins, EFG and PDGF etc. to

ameliorate defective, diseased or damaged neurons, such as neurons associated with PD or AD, in the mammalian brain *in vivo*.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen